SCIENTIFIC SECTION

A COMPARATIVE STUDY OF THE PHARMACOLOGICAL ACTIONS OF NATURAL AND SYNTHETIC CAMPHOR.*,[1]

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INTRODUCTION.

During the past several years camphor has acquired an especial interest because of the wide divergence of opinion concerning its pharmacological behavior and clinical efficiency and more recently because of the growing tendency to replace natural products by synthetically prepared materials which are identical in physical and chemical properties. The replacement of natural Japanese camphor by synthetic camphor has occurred quite extensively in the industries and the synthetic form has been included in the eleventh revision of the United States Pharmacopœia.

Some observers are of the opinion, based on experimental evidence, that no difference whatever exists between natural camphor and synthetic camphor in their pharmacologic actions and on this basis can see no reason why synthetic camphor cannot replace natural camphor in therapeutics. On the other hand, others claim that synthetic camphor is more toxic than the natural product and should not be used unless absolutely necessary and then only cautiously.

The published clinical reports on synthetic camphor are few and the details somewhat meager. Some clinicians feel that it is fully as effective as natural camphor in cardiac and circulatory diseases and the replacement of natural camphor by the synthetic product fully justifiable. On the other hand, other investigators feel that on the basis of the experimental results which show that the synthetic camphor is more toxic than natural camphor and the absence of adequate clinical reports, the substitution of synthetic camphor for natural camphor in therapeutics seems unwarranted where no absolute necessity exists or at any rate until further observations are made and the discrepancies in the evidence cleared up. These experimental and clinical contradictions and disagreements prompted the undertaking of this study.

DIFFERENCES OF OPINION CONCERNING THE PHARMACOLOGICAL ACTIONS.

The earliest investigators on this subject, Langaard and Maass (1), using preparations of dextro, lævo and racemic camphor were able to obtain an excitation of the central nervous system in frogs with all three forms. They found that in this respect the lævo was the most powerful, the dextro the least, and the racemic intermediate between the two.

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Pari (2) showed lævo camphor to be thirteen times more toxic than the dextro form and concluded that inasmuch as synthetic camphor is composed of a mixture of both dextro and lævo camphor the racemic compound would be more toxic than the natural dextro camphor. This point particularly emphasized the necessity of careful research before the synthetic camphor can be considered therapeutically equivalent to the natural dextro camphor.

Sargin (3) maintains that all three isomers of camphor have a similar action. However, he found the fatal dose of lævo camphor to be 20 per cent smaller than that of dextro camphor.

Joachimoglu (4), one of the foremost workers in this field, compared the three stereoisomers of camphor and concluded that no difference exists between them in regard to toxicity and that the synthetic camphor is tolerated by the organism just as well as is the dextro form.

Joachimoglu (5) in further work using smooth muscle of the leech found that the three isomers produced qualitatively and quantitatively the same effect.

Ramirez (6) concluded that the pharmacodynamic similarity of natural and synthetic camphor as regards their effects on the blood pressure, renal output, respiration, vessels and hearts of frogs and dogs is so great that no differences may be established between them using the current methods of investigation. On the basis of his experimentation Ramirez claims that this similarity would justify the use of either one of the camphors in clinical work.

EXPERIMENTAL.

Relative Toxicities of Synthetic and Natural Camphor.—In order to determine the relative toxicities of synthetic and natural camphor a series of experiments were performed using white rats.

The minimum lethal dose of synthetic camphor for white rats was found to be smaller than that of natural camphor; namely, synthetic camphor 1.7 mg./Gm. (Table I), and natural camphor 2.2 mg./Gm. (Table II). The accompanying tables include the experiments just above and below the found minimum lethal doses. In order to facilitate the tabulation of the results it was found convenient to note the time after the injection required for the appearance of the first symptom such as jerking and trembling, the time after the injection for the first convulsion to occur and also the time required to produce death.

TABLE I.—MINIMUM LETHAL DOSE OF SYNTHETIC CAMPHOR FOR WHITE RATS. THE CAMPHOR, IN A 20 PER CENT SOLUTION IN OLIVE OIL, INJECTED UNDER THE SKIN OF THE BACK OR FLANK. "R"—RECOVERY. "D"—DEATH.

Rat No.	Wt. in Grams.	Milligrams per Gram Injected.	Milligrams Injected.	First Symptom, Minutes.	First Convulsion, Minutes.	Death or Recovery in Hours.
5	156	1.5	234	13	68	R
7	156	1.6	251	17	33	R
*10	132	1.7	224	20	24	D-27.5
17	178	1.8	320	21	31	D-25.0
21	262	2.0	524	21	50	D-19.5

* M. L. D.

TABLE II.—MINIMUM LETHAL DOSE OF NATURAL CAMPHOR FOR WHITE RATS. THE CAMPHOR, IN A 20 PER CENT SOLUTION IN OLIVE OIL, INJECTED UNDER THE SKIN OF THE BACK OR FLANK. "R"—RECOVERY. "D"—DEATH.

Rat No.	Wt. in Grams.	Milligrams per Gram Injected.	Milligrams Injected.	First Symptom, Minutes.	First Convulsion, Minutes.	Death or Recovery in Hours.
1	112	2.1	235	6	32	R
* 7	180	2.2	396	42	55	D-42
13	260	2.3	598	24	35	D-30
19	229	2.4	549	17	40	D-31.5
21	157	2.6	408	9	34	D-28

* M. L. D.

These experiments also indicated that the action of synthetic and natural camphor is primarily upon the central nervous system and that there is no qualitative difference in their action. However, quantitatively there is considerable difference in that the minimum lethal dose of synthetic camphor is 1.7 mg. per Gm. of body weight of rat while that of natural camphor is 2.2 mg. per Gm. of body weight of rat. Further, the action of synthetic camphor develops more rapidly and causes death sooner than does natural camphor. Death with both kinds of camphor is due to respiratory failure.

Action of Synthetic Camphor on the Normal Frog Heart.—A 1–1000 solution of synthetic camphor in 0.6 per cent salt solution and frogs weighing from 20 to 30 Gm. were used. In order to eliminate the temperature factor the frogs and all solutions used were kept at room temperature. One cc. of the 1–1000 solution was dropped on the exposed frog heart at intervals of 15 minutes and short tracings taken at intervals of 3 minutes.

Synthetic camphor has a marked effect on the rate and amplitude of the frog heart. (Fig. 1 and 2.)

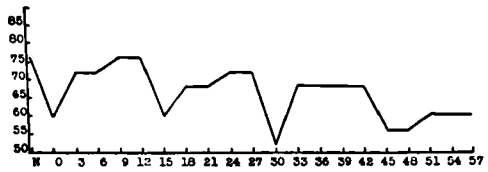

Fig. 1.—Rate curve of typical effect of synthetic camphor, 1–1000 solution, on the normal frog heart (Exp. 1). Ordinate: Beats per minute; Abscissa: Time in minutes; N: Normal. Synthetic camphor applied at N, 12, 27 and 42.

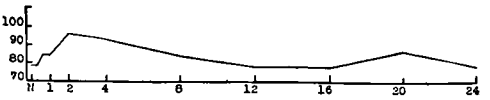

Fig. 3.—Rate curve showing typical effect of perfusing the isolated rabbit heart with a 1–5000 solution of synthetic camphor (Exp. 54). Ordinate: Beats per minute; Abscissa: Time in minutes; N: Normal. Synthetic camphor solution perfused at N; replaced with Ringer's solution at 1.

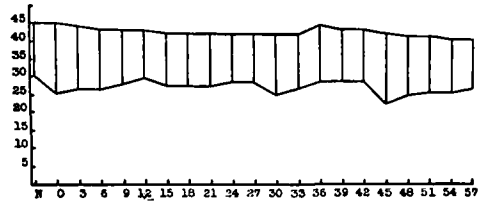

Fig. 2.—Amplitude curve of typical effect of synthetic camphor, 1–1000 solution, on the normal frog heart (Exp. 1). Ordinate: Amplitude in mm. (x 4); Abscissa: Time in minutes; N: Normal. The vertical lines represent the height of a tracing made with a lever attached to the ventricle of the frog heart and also its relation to the base line. Synthetic camphor applied at N, 12, 27 and 42.

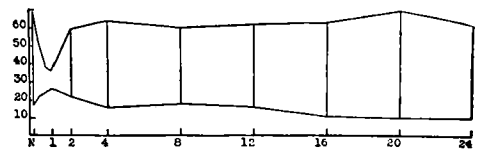

Fig. 4.—Amplitude curve showing the typical effect of perfusing the isolated rabbit heart with a 1–5000 solution of synthetic camphor (Exp. 54). Ordinate: Amplitude in mm.; Abscissa: Time in minutes; N: Normal. Synthetic camphor solution perfused at N; replaced with Ringer's solution at 1.

The heart rate was found to decrease and then increase but not back to the normal level. As the experiments proceeded and more synthetic camphor was ad-

ministered the rate decrease from the high level of the preceding period became less, but still dropped more and more below the normal. Decrease in rate varied from 4 to 28 beats per minute. The amplitude of the excursion of the frog heart showed an increase to above normal, either staying there or falling back to the normal level after a short time. The increases in the amplitude were usually in the diastolic direction. It was noted that the slowing of the beat of the normal frog heart by synthetic camphor was compensated for by the increase in the amplitude, thus producing a slower but stronger beat. The progression toward the diastolic line indicates a loss of muscle tone.

Action of Natural Camphor on the Normal Frog Heart.—The same procedure was followed as in the preceding but with a 1–1000 solution of natural camphor.

It was found that natural camphor had some effect on the rate and amplitude although it was not as pronounced as that produced by synthetic camphor.

Following the first application of natural camphor to the frog heart the rate decreased. Decrease in rate varied between 4 and 24 beats per minute. The decrease in rate was followed by an increase but the normal rate was never regained. Second, third and fourth applications produced essentially the same effect as the first, the rate decreasing in every instance from that of the preceding.

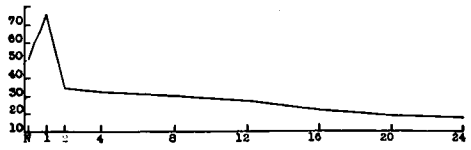

Fig. 5.—Curve showing the typical effect on the coronary flow of perfusing the isolated rabbit heart with a 1–5000 solution of synthetic camphor (Exp. 54). Ordinate: Cc. per minute; Abscissa: Time in minutes; N: Normal. Synthetic camphor solution perfused at N; replaced with Ringer's solution at 1.

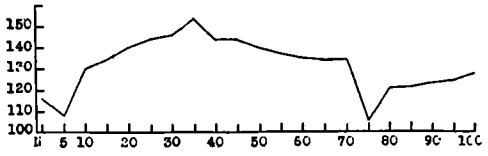

Fig. 6.—Blood pressure curve showing the typical effect of intravenous injections of synthetic camphor on the cat (Exp. 73). Injections: 5 mg./Kg. at N; 10 mg./Kg. at 35; 20 mg./Kg. at 70. Ordinate: Blood pressure in mm. of Hg; Abscissa: Time in minutes; N: Normal.

The first application of natural camphor caused an increase in the amplitude of the excursion of the frog heart and in all cases the increase was toward the diastolic lines.

A second, third and fourth application produced essentially the same effect as the first application, the amplitude increasing in every instance from the preceding period. This increase varied from 1 to 3.5 mm. and was toward the diastolic line in every case.

From the data herein presented it will be seen that although the action of the two camphors is essentially the same qualitatively, the synthetic camphor has a more powerful action on the normal frog heart in slowing the beat and increasing the amplitude of the excursion than has natural camphor.

Action on the Isolated Perfused Rabbit Heart.—For perfusing the isolated rabbit heart the method and apparatus of Gunn (7) was used.

Varying concentrations of synthetic camphor in Ringer's solution were used, *i. e.*, 1–1000, 1–5000 and 1–10,000, several experiments being carried out with each concentration. After a

normal tracing was obtained the synthetic camphor solution was turned on and allowed to remain on until the point of maximum effect was reached when the Ringer's solution was again turned on, replacing the synthetic camphor solution.

Perfusion of the isolated rabbit heart with varying concentrations of *synthetic* camphor produced an immediate increase in *rate.* Upon changing to Ringer's solution this increase in rate was followed in every instance by a fall back to or below normal and this in turn was followed by an increase back to or slightly above the normal rate. The greatest changes in rate were produced by the strongest solution (1–1000) and the least by the weakest solution (1–10,000). (Fig. 3.)

With respect to the *amplitude,* all concentrations of synthetic camphor used produced a distinct fall. The fall was the greatest with the 1–1000 solution and the least with the 1–10,000 solutions. The initial fall was followed by an increase to above normal when the synthetic camphor solution was replaced by Ringer's solution. This increase was maintained at or above the normal until the end of the experiment. (Fig. 4.)

With all concentrations used the initial change in amplitude was in the diastolic direction. Replacement of the synthetic camphor solution with Ringer's solution produced an increase in the systolic direction.

All concentrations of synthetic camphor used produced an increase in the coronary output in all the experiments performed, the extent of increase being in the direction of the greatest concentration. Replacement of the synthetic camphor solution with Ringer's solution produced in all cases a decrease in the rate of flow back to or below the normal. (Fig. 5.)

The initial fall in amplitude is compensated for by the initial increase in the rate and the fall in rate is in turn compensated for by the increase in amplitude. The amplitude change in the diastolic direction indicates a loss of muscle tone while the recovery in the systolic direction suggests a stronger and more complete contraction, indicating perhaps an increase in the tonicity of the cardiac muscle.

From the above it will be seen that after an initial, pronounced depressant effect, synthetic camphor stimulates slightly the heart of the rabbit, the action presumably being on the heart muscle. The coronary vessels exhibit a dilation due to the effect of the synthetic camphor. This dilation is then followed by a constriction, as evidenced by the decreased coronary output.

The same procedure was followed using natural camphor. All concentrations of *natural* camphor when perfused through the isolated rabbit heart produced an immediate increase in *rate.* The greatest changes in rate were produced by the strongest concentrations.

The *amplitude* of the rabbit heart with all concentrations used suffered a marked fall in all cases and again the strongest solution produced the greatest effect. The direction of the amplitude change was in the diastolic direction. Replacement of the natural camphor solution with Ringer's solution brought about recovery in the systolic direction.

Perfusion with all concentrations produced an increase in the *coronary* output, the greatest increase occurring with the strongest solution. This increase indicates a dilation of the coronary vessels. Increase was followed by a gradual decrease to below the normal, due perhaps to a constriction of the coronary vessels.

The initial fall in amplitude is compensated for by the increase in rate and

the fall in rate by the increase in amplitude. That the coronary vessels are dilated is indicated by the increased flow. This, however, is followed by a constriction, thus producing the diminished flow which was observed.

From the above it will be seen that the action of synthetic and natural camphor on the perfused isolated mammalian heart is essentially qualitatively alike. However, that synthetic camphor has a more powerful action is evident from the more pronounced changes in rate, amplitude, coronary flow and the shorter time required to produce these changes. With synthetic camphor the heart appeared to have an improved tonicity in that at the end of every experiment the heart was in a state of greater contraction than the normal, whereas, with natural camphor only a few were in a state of greater contraction at the conclusion of the experiment than when normal and then only slightly so.

Action on the Mammalian Circulation and Respiration.—Cats anesthetized with urethane, 0.9 Gm./Kg. orally about a half-hour before the operation, were used in these experiments. During the operation it was found advisable to give a little ether.

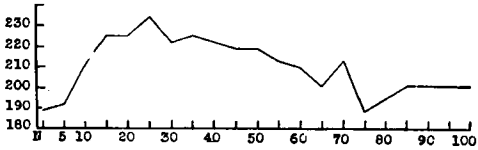

Fig. 7.—Heart rate curve showing the typical effect of intravenous injections of synthetic camphor on the cat (Exp. 73). Injections: 5 mg./Kg. at N; 10 mg./Kg. at 35; 20 mg./Kg. at 70. Ordinate: Heart rate per minute; Abscissa: Time in minutes; N: Normal.

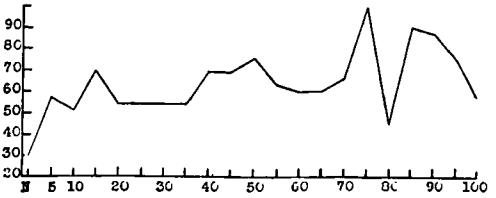

Fig. 8.—Respiratory rate curve showing the typical effect of intravenous injections of synthetic camphor on the cat (Exp. 73). Injections: 5 mg./Kg. at N; 10 mg./Kg. at 35; 20 mg./Kg. at 70. Ordinate: Rate per minute; Abscissa: Time in minutes; N: Normal.

For the intravenous injections the femoral vein was exposed and a cannula, attached by means of a short rubber tube to a burette containing Normal Salt Solution, tied in. Injections were made through the walls of the rubber tube and the solution washed into the vein by letting in a little salt solution. All injections were kept below 2 cc. in volume.

Intravenously, doses of 5, 10 and 20 mg. of *synthetic* camphor in a 1 or 2 per cent solution in olive oil per Kg. of cat were administered, thus taking care not to give a convulsive dose. The dose of 5 mg./Kg. was calculated to be about equivalent to the usual subcutaneous dose in man.

Following the intravenous injection of 5 mg./Kg. the blood pressure, after a slight preliminary fall, rose to above the normal where it remained until the end of the 30-minute period. (Fig. 6.) The preliminary fall occurred in from 1 to 3 minutes and ranged between 2 and 8 mm. of Hg. After 2 to 10 minutes the blood pressure returned to normal and above, and 30 minutes after the injection was between 8 and 30 mm. of Hg. above the normal level. The intravenous injection of 10 mg./Kg. produced a similar although more pronounced effect. (Fig. 6.)

The injection of 20 mg./Kg. produced in all instances a marked fall in blood pressure of from 31 to 100 mm. in from 1 to 3 minutes. This was then followed in all cases by a rise but the blood pressure after 30 minutes, remained considerably below the original normal. (Fig. 6.)

Following intravenous injection of 5 mg./Kg., the heart rate, after a slight preliminary fall of from 3 to 6 beats per minute, increased gradually and at the end of the half-hour period was from 21 to 33 beats per minute above the normal. (Fig. 7.)

The injection of 10 mg./Kg. intravenously produced in about half of the experiments a preliminary fall followed by a still greater rise than was noted after the first injection. In the other experiments the rate after a slight increase fell steadily.

The intravenous injection of 20 mg./Kg. produced in the majority of the experiments an immediate and marked fall in heart rate to considerably below the original normal. This was then followed by an increase up to or slightly below the normal. (Fig. 7.)

The intravenous injection of 5 mg./Kg. caused an immediate increase in the *respiratory* rate. This was then followed by a decrease but at the end of the period the respiration was still above the normal. (Fig. 8.) The maximum rate was reached in about 2 or 3 minutes and ranged between 12 and 39 inhalations (or exhalations) per minute. The depth of the respiration was also increased.

The injection of 10 mg./Kg. produced very much the same effect except that it was more pronounced and more prolonged.

With 20 mg./Kg. a still greater and more prolonged effect was produced than with the former injections. In all the experiments the respiratory rate increased immediately, reaching the maximum in from 1 to 2 minutes, the rate increase ranging between 39 and 93 inhalations per minute. (Fig. 8.) The depth of the respiration again showed an appreciable increase over the former injections.

The *blood pressure* of the cat following the intravenous injection of synthetic camphor behaved according to the dose administered. Small doses, 5 mg./Kg., which approximates the usual human subcutaneous dose, produced, after a slight preliminary fall, a considerable increase in the blood pressure. Larger doses, 10 mg./Kg., as a rule produced a fall in blood pressure although the blood pressure still remained above the normal. With still larger doses, 30 mg./Kg., the blood pressure suffered a marked fall, the subsequent rise not regaining the normal level.

After subcutaneous injections of synthetic camphor, 0.2 Gm./Kg., a gradual increase in blood pressure was observed. This was followed by a gradual fall to below the normal level in from 30 to 50 minutes where it remained until the end of the two-hour period. Absorption was apparently complete in from 30 minutes to 1 hour. The effect came on slower but was more prolonged than with the intravenous injections.

The increase in blood pressure following the intravenous injection of 5 mg./Kg. may possibly be accounted for by the increased heart rate, the increased rate being due to a direct stimulation of the heart muscle since it has been shown in previous experiments that perfusion of the isolated mammalian heart with varying concentrations of synthetic camphor produced an increase in heart rate. The fall in blood pressure following the administration of a larger dose, 10 mg./Kg., despite the fact that the heart rate still increased, is probably due to a direct systemic vasodilator effect. It will be remembered that the coronary blood vessels of the isolated mammalian heart were dilated after perfusion with solutions of synthetic camphor. The still greater fall in blood pressure after the intravenous injection of 20 mg./Kg. might be attributed to a more pronounced vasodilator effect and also to the marked slowing of the heart which was evident. This slowing may be due to a direct depres-

sant effect on the heart muscle since the concentration of synthetic camphor in the system had reached a rather high level after the last injection.

Similarly the increase in blood pressure following the subcutaneous injection of synthetic camphor, 0.2 Gm./Kg., might be attributed to the increased heart rate. The fall which occurred can likewise be attributed, despite the increased heart rate, to a systemic vasodilator action in that absorption was usually complete in from one-half to one hour and about this time the blood pressure began to fall and continued to do so until, after two hours, it was considerably below the normal level.

The most pronounced and consistent effect of synthetic camphor was noted on the respiration. The intravenous injection of all doses, 5, 10 and 20 mg./Kg., produced in every instance an immediate and marked increase in the depth and rate of respiration. The largest dose, 20 mg./Kg., produced the most pronounced and lasting effect and conversely, the smallest dose, 5 mg./Kg., the least effect. However, in almost every instance, regardless of the dose administered, the respiratory rate at the conclusion of the experiment was still above the normal.

With subcutaneous injections of synthetic camphor, 0.2 Gm./Kg., the same effects on the respiration were noted as in the case of the intravenous injections except that they were not as pronounced nor did they come on as quickly. However, the effect was more prolonged.

The same procedure was followed as in the preceding, using *natural* camphor solutions. It was observed that natural camphor produced qualitatively similar effects but that synthetic camphor is more potent quantitatively.

The comparative effects of synthetic and natural camphor upon the mammalian circulation and respiration may be summarized as follows:

A.—After small intravenous doses, synthetic camphor produces a marked stimulation of the circulatory system as shown by the increased blood pressure due possibly to an increased heart rate which may be due to a direct action on the heart muscle and despite any vasodilation. Natural camphor, on the other hand, after small intravenous doses, produces a more or less depressant effect on the circulation as shown by the fall in blood pressure due perhaps to a systemic vasodilation and despite the increased heart rate.

B.—Larger intravenous doses of both synthetic and natural camphor produce a marked depression of the mammalian circulation as evidenced by the marked lowering of the blood pressure and decrease in heart rate. The effect of synthetic camphor is more prompt, more pronounced and more lasting than that of natural camphor.

C.—Synthetic camphor, subcutaneously, after a more or less brief stimulant effect on the circulation as shown by the increased blood pressure, due possibly to an increased heart rate despite any vasodilation, has a depressant effect on the mammalian circulation as shown by the decrease in blood pressure due possibly to an increased vasodilation and despite the increased heart rate. Natural camphor, on the other hand, after subcutaneous injections has a marked depressant effect as shown by the fall in blood pressure due possibly to a systematic vasodilation and despite the increased heart rate. The effects of synthetic camphor here also are more pronounced than those of natural camphor.

D.—Both synthetic and natural camphor, intravenously and subcutaneously, have a marked stimulant effect on the mammalian respiration as shown by the increased rate and depth. However, the effects of synthetic camphor are more pronounced and more lasting than those of natural camphor.

SUMMARY AND CONCLUSIONS.

1. The minimum lethal dose of synthetic camphor for white rats is 1.7 mg. per Gm. while that of the official natural camphor is 2.2 mg. per Gm. of body weight

of rat. Both synthetic and natural camphor act chiefly on the central nervous system, death being due to respiratory paralysis.

2. Both synthetic and natural camphor cause a depressant action on the normal frog heart.

3. Neither synthetic camphor nor natural camphor is of value in overcoming the effect of chloral hydrate on the frog heart.

4. Both synthetic camphor and natural camphor primarily depress the perfused isolated mammalian heart.

5. The effect of intravenous and subcutaneous injections of both synthetic and natural camphor on the circulation is chiefly depressant.

6. Both synthetic and natural camphor markedly stimulate the mammalian respiration.

7. The differences in action between synthetic camphor and natural camphor are chiefly quantitative and not qualitative, synthetic camphor having a more pronounced and powerful action.

8. It appears logical and justifiable from the experimental evidence obtained to substitute synthetic camphor for natural camphor for medicinal purposes.

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THE ANTHRONE DERIVED FROM BARBALOIN AND ISOBARBALOIN.*

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More than twenty years ago, Léger (1) presented evidence that the common varieties of aloin are mixtures of two isomers, barbaloin and isobarbaloin. The aloin sold in this country is prepared from Curaçao aloe and is made up largely of barbaloin with a smaller but still considerable proportion of isobarbaloin.

These isomers resemble each other closely in most of their properties. They have the same percentage composition, melting point and crystal form. The most notable differences are, *first*, isobarbaloin is much more soluble in methyl alcohol than is barbaloin, and *second*, isobarbaloin gives a Klunge reaction (a red color with aqueous sodium chloride and copper sulfate) in a few minutes whereas with barbaloin the color appears only after a half hour or longer. Léger also describes a number of cases in which the corresponding derivatives of the two substances dif-

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